Effects of Electroacupuncture on Opioid-induced Constipation in Patients with Cancer: A Randomized Controlled Trial

Statistical Analysis Plan
(Final 1.0)

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1. Introduction

About 70-80% of patients experience moderate to severe pain. As the cornerstone of treatment for moderate to severe cancer pain, opiate analgesics, such as morphine and oxycodone, are recommended by WHO Cancer Pain Relief Guidelines. The use of systemic opioids is recommended by some studies for cancer patients experiencing moderate to severe pain, regardless of the underlying causes. Opioids stimulate receptors both in the central nervous system (CNS) and the peripheral nervous system, reducing pain and improving quality of life for patients. The drug can, however, be associated with serious adverse events (AEs) with a rate ranging from 1.8% to 13.6%, the most common of which is opioid-induced constipation (OIC). OIC represents a change in baseline bowel habits or defecation patterns that occurs following the administration or modification of opioid therapy. Approximately 41% of non-cancer patients and 94% of cancer patients who use opioids for pain have this condition. Symptoms of OIC are usually persistent and difficult to tolerate, which adversely affects patients' quality of life and results in reductions in dose or discontinuation of opioid analgesics. OIC is the result of multiple factors contributing to it: Opioids may activate μ-receptors throughout the gastrointestinal tract and cause changes to gut motility, decreases in gut secretion, and an increase in sphincter tone, which can lead to constipation. Various pharmacological and nonpharmacological interventions are used to manage OIC, such as laxatives and increased fluid intake. However, these interventions are limited in effectiveness, and they do not address the pathophysiological mechanisms of OIC. However, longer-term efficacy and safety of PAMORAs are unclear, and they haven't been approved in China yet. Clinical trials are still underway to test these drugs. Additionally, PAMORAs are often associated with AEs such as abdominal pain and flatulence. As a result, it is still necessary to explore new treatment approaches for OIC.

Acupuncture has been used to treat gastrointestinal disease, including constipation, for thousands of years. According to two systematic reviews, acupuncture can improve spontaneous bowel movements (SBMs) in functional constipation. Additionally, the results of our study indicated that electroacupuncture (EA) could increase complete spontaneous bowel movements (CSBMs) and SBMs, with a long-term effect that continues for 24 weeks after treatment ceased among patients with chronic, severe

functional constipation. Through stimulation of the somatic and peripheral nervous systems, acupuncture can facilitate the gut motility and improve gastrointestinal function. The effectiveness of acupuncture for OIC is currently lacking evidence.

2. Study objective

The objective of this study is to assess the efficacy of EA for OIC in adult patients with cancer pain.

3. Design

This is a multicenter, sham-controlled, assessor-blinded, randomized trial.

4. Statistical Considerations

4.1 Study Hypothesis

The primary study hypothesis is that EA is more effective than SA in patients with cancer pain.

4.2 Statistical Hypothesis

The null hypothesis is that the proportion of responders will be the same for EA and SA, and the alternative hypothesis is that the change would differ.

4.3 Study Populations

All patients with randomization will be included in the analysis set regardless of whether they receive any treatment. According to the intention-to-treat principle, all analysis will be based on the randomization set.

4.4 Statistical Analyses

4.4.1 The General Principle

Summary tables (descriptive statistics and/or frequency tables) will be provided for all variables at different endpoints. For continuous variables, means and standard deviations will be presented, unless the variable has a skewed distribution, in which case medians, 25th and 75th percentiles will be presented. For categorical variables, the number and percentage of participants within each category will be presented. For each variable (continuous or categorical), the number of missing values will be reported.

Statistical Comparisons Between Groups

Continuous variables will be compared using a two-sample *t*-test or Wilcoxon rank-sum test if data show serious deviations from a normal distribution. Categorical data or ordinal data will be compared using a Wilcoxon rank-sum test, chi-square test or Fisher's exact test, as appropriate. All tests will be two-sided.

For the analysis of the primary and secondary outcomes, estimated treatment differences and associated 95% two-sided confidence intervals will be presented.

Analysis Software

For all statistical analyses, SAS 9.4 software will be used. All hypothesis testing will be carried out at the 5% (2-sided) significance level.

4.4.2 Demographics and Baseline Characteristics

All data recorded at baseline will be summarized by group. Comparisons between groups will be performed using the methodology described in section 4.4.1. Summaries will be presented for the ITT Set in both groups.

4.4.3 Analyses for Primary Outcome

The primary outcome will use a generalized linear model with a binomial distribution and identity link. The subgroup analysis will be conducted by adding an interaction between the baseline daily opioid dose and treatment into the generalized linear model.

As a sensitivity analysis, missing data on the primary outcome will be imputed using the multiple imputation method under the missing at random assumption.

4.4.4 Analyses for Secondary Outcomes

Efficacy analyses for all secondary outcomes will be performed in the ITT population, without imputation of missing data.

Continuous data will be described with the average, standard deviation, median, minimum value, and maximum value, whereas categorical data will be represented by percentages as appropriate.

4.4.5 Safety Analyses

All adverse events and serious adverse events will be listed. Adverse events include the acupuncture-related adverse events and other adverse events.

5. The Summary of Changes of Final SAP

As compared to the original statistical analysis plan (SAP) published in the *Front. Med.* (Zhishun Liu, Yang Wang, Huanfang Xu, et al. Effects of Electroacupuncture on Opioid-Induced Constipation in Patients with Cancer: Study Protocol for a Multicenter Randomized Controlled Trial. Front Med. 2022), the present finalized SAP had made a few amendments. The major updates were provided in Table 1.

Table 1. MAJOR UPDATES OF THE ORIGINAL SAP

No.	Item	Original Version	Final Version
1	Missing data	Missing data on the primary outcome will be imputed using the multiple imputation method under the missing at random assumption.	**As a sensitivity analysis,** missing data on the primary outcome will be imputed using the multiple imputation method under the missing at random assumption.
2	Primary outcome	The primary outcome will be evaluated using **the x^2 test.**	The primary outcome will use **a generalized linear model** with a binomial distribution and identity link.
3	Safety outcome	AE incidences for each treatment group will be compared using **Fisher's exact test**.	AE data will be provided for **descriptive purposes only.**